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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,151	10/30/2001	Jeffrey R. Balser	1242/49/2	8248

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JENKINS, WILSON & TAYLOR, P. A.
3100 TOWER BLVD
SUITE 1200
DURHAM, NC 27707

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,151	BALSER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-19 and 100-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-19 and 100-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2005 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 31 October 2005 has been entered in full. Claims 1, 9-13, 15-17 are amended. Claims 4-8 and 20-99 are cancelled. Claims 100-104 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 9-19, and 100-104 are under consideration in the instant application.

Information Disclosure Statement

The supplemental information disclosure statement filed on 29 April 2005 has been considered.

Claim Rejections - 35 USC § 112, second paragraph

1. Claims 1-3 and 9-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. The term "biologically active" in claims 1-3 and 9-19 is a relative term which renders the claims indefinite. The term "biologically active" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the

art would not be reasonably apprised of the scope of the invention. It is not clear from the claims and the specification what *specific* activity or activities of HERG, KCR1, and miRP1 the claims encompass.

Claim Rejections – 35 U.S.C. § 112, first paragraph

3. Claims 1-3, 9-19, and 100-104 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that modulates potassium transmission by a potassium channel comprising: (a) providing a structure comprising a human ether-a-go-go-related gene (HERG) potassium channel polypeptide comprising *the* amino acid sequence of SEQ ID NO: 3 and a potassium channel regulator 1 (KCR1) polypeptide comprising *the* amino acid sequence of SEQ ID NO: 2; (b) contacting the cell with the structure; (c) determining potassium transmission by the HERG channel in the presence of the test compound; and (d) comparing the potassium transmission by the HERG channel in the presence of the test compound to the potassium transmission by the HERG channel in an absence of the test compound, wherein a difference between potassium transmission by the HERG channel in the absence of the test compound and potassium transmission by the HERG channel in the presence of the test compound indicates modulation of potassium transmission by the HERG channel, *does not reasonably* provide enablement for a method of identifying a compound that modulates potassium transmission by a potassium channel comprising: (a) providing a structure comprising a human ether-a-go-go-related gene (HERG) potassium channel polypeptide comprising an amino acid sequence at least 90% or 99% identical to SEQ ID NO: 3 and a biologically active potassium channel regulator 1 (KCR1) polypeptide comprising an amino acid sequence at least 90% or 99% identical to SEQ ID NO: 2; (b) contacting the cell with the structure; (c) determining potassium transmission by the HERG

channel in the presence of the test compound; and (d) comparing the potassium transmission by the HERG channel in the presence of the test compound to the potassium transmission by the HERG channel in an absence of the test compound, wherein a difference between potassium transmission by the HERG channel in the absence of the test compound and potassium transmission by the HERG channel in the presence of the test compound indicates modulation of potassium transmission by the HERG channel. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 3-12 of the Office Action of 29 October 2004 and at pg 3-6 of the Office Action of 10 November 2003.

The claims also recite that the structure is a cell and that the cell is isolated from a subject. The claims recite that the biologically active KCR1 polypeptide is encoded by a nucleic acid selected from the group consisting of SEQ ID NO: 1 and nucleic acids that differ from SEQ ID NO: 1 only by virtue of genetic code redundancy. The claims also recite that the determining comprises employing a patch clamp apparatus and that the biological activity of a structure comprising a potassium channel polypeptide and a KCR1 polypeptide in the presence of a test compound is determined in the presence of a biologically active MiRP1 polypeptide. The claims recite that the biologically active MiRP1 polypeptide comprises an amino acid sequence at least 90% identical to SEQ ID NO: 5.

Applicant's arguments (31 October 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive.

(i) At page 8 of the Response, Applicant asserts that one of ordinary skill in the art would be capable of generating nucleic acids and polypeptides that are at least 90% identical to SEQ ID

NO: 2, 3, and 5, based on the teachings of the instant disclosure. Applicant contends that the Patent Office has not provided any support for the contention in the Advisory Action that the experimentation would be undue, only that it might be complex. Applicant cites MPEP § 2164.01. Applicant argues that given the teachings of the specification concerning the functional assays for the structure comprising a biologically active human HERG potassium channel polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 3 and a biologically active KCR1 polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 2, one of ordinary skill in the art would be able to generate and test nucleic acid and polypeptide variants using only routine, and not undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. First, it is noted that the specification of the instant application teaches that the term "polypeptide" means any polymer comprising any of the 20 protein amino acids, regardless of size (pg 14, lines 31-32). Thus, claims 1-3, 9-19, and 100-104 are broadly interpreted by the Examiner as reading upon: (i) protein and DNA variants with any number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NOs: 2, 3, and 5, including sequences only 2 amino acids in length. However, the specification does not teach any variant, fragment, or derivative of the HERG, KCR1, and miRP1 proteins and polynucleotides other than the full-length amino acid sequences and the full-length nucleic acid sequences. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the

protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). For example, Lehmann-Horn et al. also discuss several point mutations in the HERG gene that cause long Q-T syndrome 2 (pg 1348, col 2 through pg 1349, col 1; Table 10). Anson et al. (Am J Physiol Heart Circ Physiol 286: H2434-2441, 2004), who studied five different HERG channels (four polymorphisms and wild-type) even state that "[f]unctional analysis is a key step to understanding the impact of amino acid coding variants on protein function" (pg H2439, col 2, 1st full paragraph). Anson et al. teach that their data suggest some HERG polymorphisms are wild-type channel-like in their physiological properties, whereas other have detectable differences (pg H2440, col 2, 2nd paragraph). Anson et al. also disclose that the COOH terminal of HERG channels may be involved in multiple aspects of channel physiology and that this unexpected role of the HERG COOH terminal region stresses the importance of functional characterization of genetic variants (pg H2440, col 1, 1st full paragraph). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a

starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Lehmann-Horn et al. also discuss several of the mutations in the HERG gene that cause long Q-T syndrome 2 (pg 1348, col 2 through pg 1349, col 1).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

3. Claims 1-3, 9-19, and 100-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set for at pg 13-16 of the previous Office Action (29 October 2004) and at pg 7-8 of the Office Action of 10 November 2003.

Applicant's arguments (31 October 2005), as they pertain to the rejection have been fully considered but are not deemed to be persuasive.

(i) At page 10 of the Response, Applicant asserts that the phrase "biologically active" in the claims encompasses that the polypeptides in the assays combine to produce a functional potassium channel. Applicant submits that there is amble support for the phrase "biologically active" in the specification, particularly when in context of the specification by one skilled in the art. Applicant also contends that other members of the HERG, KCR1, and miRP1 families have been disclosed in the art. Applicant indicates that Genbank Accession Nos. NP_001003145 (dog), NP_038597 (mouse), AAB68612.1 (rabbit), and NP_446401.1 (rat) relate to HERG channel polypeptides; NP_620801 (rat), XP_534842.2 (dog), XP_589768.2 (cow), and BAE38718.1 (mouse) relate to KCR1 polypeptides. Applicant also states that NP_598287.1 (rat), XP_531544 (chimpanzee), AAK15527 (rabbit), and NP_598871 (mouse) correspond to miRP1 family members. Applicant adds that several of these sequences are at least 90% identical to one of SEQ ID NOs: 2, 3, and 5.

Applicant's arguments (31 October 2005), as they pertain to the rejection have been fully considered but are not deemed to be persuasive. First, it is noted that the specification of the instant application teaches that the term "polypeptide" means any polymer comprising any of the 20 protein amino acids, regardless of size (pg 14, lines 31-32). Thus, claims 1-3, 9-19, and 100-104 are broadly interpreted by the Examiner as reading upon: (i) protein and DNA variants with any number of deletions, substitutions, or additions and (ii) fragments of SEQ ID NOs: 2, 3,

and 5, including sequences only 2 amino acids in length. Specifically, Applicant has not described or shown possession of all polypeptides 90% homologous to SEQ ID NOs: 2, 3, and 5, that still retain the function of SEQ ID NOs: 2, 3, and 5. Nor has Applicant described a representative number of species that have 90% homology to SEQ ID NOs: 2, 3, and 5, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 2, 3, and 5. The specification of the instant application only teaches a human HERG channel of SEQ ID NO: 3, a KCR1 polypeptide of SEQ ID NO: 2, and a miRP1 polypeptide of SEQ ID NO: 5. The broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a recitation of percent identity (90%, 99%). There is no identification of any particular portion of the structure that must be conserved in order to conserve the required function or that the described function is truly representative of all members of the claimed genus. There is also no identification of a specific physiological function that must be conserved among the HERG, KCR1, and miRP1 variants. Clearly, such

does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Therefore, only a polypeptide comprising *the* amino acid sequence of SEQ ID NOs: 2, 3, and 5 or a polypeptide comprising an amino acid sequence that is at least 99% identical to SEQ ID NOs: 2, 3, 5 with a specific functional limitation, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
26 January 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER